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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,144	09/27/2004	Kurt Berlin	82309	6722

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EXAMINER	
POHNERT, STEVEN C	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,144	BERLIN, KURT	
	Examiner	Art Unit	
	STEVEN C. POHNERT	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *12-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 September 2004* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed 11/24/2008.

The sequence compliance issues have been overcome by the response.

This action is FINAL

Claim Rejections - 35 USC § 103- New Grounds Necessitated by Amendment

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-6, 9, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) and Berlin et al (WO01/27317, published 4/1/2001).

Citations from Berlin et al (WO01/27317, published 4/1/2001) refer to the National Stage (U.S. Patent No. 7,179, 594 issued 2/20/2007). The National Stage is deemed an English language translation of the PCT.

Genomic methylation pattern is interpreted to include tissue specific methylation patterns.

The amendment to the claims to recite hemimethylation requires the presence of a methylated and non-methylated strands.

The amendment of "said DNA being methylated at one or more cytosine positions" is not defined in the specification. Thus "said DNA being methylated at one or more cytosine positions" is being given the broadest reasonable interpretation of a single or double stranded DNA with at least one cytosine that is methylated.

Lopez et al teaches the amplification of genomic DNA by PCR in the presence of a DNA methyltransferase (see figure 1and page 17, lines 26-28) (claim 1) and amplification by single strand displacement amplification and methylation with a DNA methyltransferase (see page 18, line 10-16) for detection. PCR and single strand displacement amplification are interpreted as steps b-C of claim 1. The strands synthesized by chain extension or single strand displacement contain the methylated parent strand and synthesized strand, which is not methylated and thus are hemimethylated. Lopez teaches ^{3}H-s-adenosyl methionine as a methyl donor with a detectable label (see page 4, line 2) (claim 4 and 5). Lopez et al further teaches the use of anchored PCR primers on a solid matrix to create ordered maps (see page 21 lines 2-4) (claim 6). Lopez et al teaches the treatment of amplified targets with methylation sensitive restriction enzyme capable of distinguishing methylated and non-methylated cytosines (see page 32, lines 25-29).

Lopez et al does not teach the use of DNA methyltransferase that preserves methylation status of genomic DNA, providing a sample DNA with one or more methylated cytosines (claim1). Lopez does not specifically teach analyzing the methylation status to determine the methylation status of the starting sample (claim 1, step g).

Lopez et al does not teach the use of DNMT1 a maintenance methyltransferase (claims 2 and 3). However, Pradhan et al teaches the use of DNMT1 as a methyltransferase (see abstract). Pradhan teaches maintenance methylation "ensures propagation of tissue specific methylation patterns during development" (see page

33002, first column text, lines 8-10). Pradhan teaches that DNMT1 has a higher reaction velocity for hemimethylated DNA substrates (see page 3302, 2nd column, last paragraph). Pradhan thus teaches DNMT1 is a maintenance methyltransferase ensures propagation of specific methylation patterns. Pradhan further teaches cytosine methylation is important in embryonic development, carcinogenesis and genetic disease (see page 33002, 1st column of text lines 1-5). Pradhan thus teaches maintenance methylation and the methyltransferases that maintain methylation patterns are important in embryonic development, carcinogenesis and genetic disease. Pradhan teaches the use of DNA known to be methylated (page 33006, 2nd column, last paragraph).

Berlin teaches methods of distinguishing methylation changes at the 5 position of cytosine bases (column 1, lines 9-10). Berlin teaches that cytosine methylation regulates transcription, genomic imprinting and tumorigenesis (column 1, lines 33-35). Berlin teaches detection of methylation by methylation sensitive restriction digestion (column 1, lines 53-67). Berlin teaches methylation defection by bisulfite treatment (column 2, lines22-51). Berlin teaches the use of genomic DNA. Berlin further teaches 5 methylcytosine is the most common genetic modification in eukaryotic cells (1st column, lines 33-34).

Therefore it would have prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the DNMT1 methyltransferase taught by Pradhan as the methyltransferase in Lopez's method of amplification and methylation of eukaryotic genomic DNA because Pradhan teaches DNMT1 is a maintenance methyltransferase that ensures propagation of methylation patterns. It would have been

further prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the amplified DNA with the genomic methylation pattern generated by the combination of Pradhan and Lopez in the methods of detecting methylation taught by Berlin. The ordinary artisan would be motivated to use the DNMT1 of Pradhan with Lopez method of Pradhan's method of methylating and amplifying DNA because it would for the production of larger quantities of methylated DNA with the genomic methylation pattern. The artisan would be motivated to analyze the amplified DNA with the genomic methylation produced by the method of Lopez and Pradhan in the method of Berlin, because it would allow for detection of methylation patterns and thus further understanding of genomic imprinting, transcriptional regulation and tumorigenesis as taught by Berlin and Pradhan. The artisan would have a reasonable expectation of success as they are merely replacing a one methyltransferase for another in methods of amplifying and methylating DNA and using known methods of detecting methylation.

Response to Arguments

The response of 11/24/2008 asserts the artisan would have no reasonable expectation of success in combining the methods of Lopez and Pradhan (page 11). The response asserts the artisan would not have a reasonable expectation of success as the method of Lopez requires the use of a methyltransferase that recognizes a specific recognition site. This argument has been thoroughly reviewed but is not considered persuasive as Pradhan teaches that DNMT1 preferentially methylates hemimethylated cytosines of canonical CGs (33009, bottom 1st column, top of2nd column). Thus DNMT1 recognizes specific sites.

The response further asserts that Lopez teaches detection of SNPs of polymorphisms that destroy methylation sites based on sequence variation. The examiner has presented the teachings of Berlin which teach the limitation of detection of methylation as required by newly added step (g) of claim 1.

The response further asserts that as Pradhan teaches the DMNT1 recognizes CG, FG, FCG, FWG it would not allow differentiation of these recognition sites. First it is noted this appears support the examiners arguments that Pradhan teaches sequence specific recognition. Further the arguments have been thoroughly reviewed but are not considered persuasive as the claims to genomic DNA and there is no evidence of record that FG, FCG, or FWG occur in genomic DNA.

Thus as the combination of Lopez, Pradhan, and Berlin teach or suggest every limitation of the claim and the combination results in the use of known methods and reagents for their known function the artisan would have a reasonable expectation of success.

The response further asserts the artisan would not have a reasonable expectation of success as Lopez teaches amplification can be done in either subsequent reactions of the same reaction mixture. The response continues these assertion by stating that PCR amplified DNA is unmethylated. This argument has been thoroughly reviewed but is not considered persuasive as the claims require and Pradhan teaches the use of methylated DNA as the DNA sample. Thus contrary to the artisan's assertion some the amplified DNA would be hemimethylated as the methylated starting DNA would still be present and thus would provide a substrate for the

hemimethylation sensitive recognition site for the DMNT1 of Pradhan. The response continues this argument by asserting that DNMT1 is inappropriate for de novo methylation and the examiner agrees, that is the logic of using DMNT1 in the instant method is that is maintains methylation of the genomic starting material.

The response continues by asserting that Lopez and Pradhan are non-analagous art with the presently claimed invention as Lopez is drawn to a method of genotyping. The response asserts, " the presently claimed method is a method of amplification of nucleic acid." This argument has been thoroughly reviewed but is not considered persuasive as Lopez teaches PCR, which is amplification. The teachings of amplification by Lopez are relied upon in the instant method, and not the genotyping. Further the response asserts that determination of base sequences is non-analogous art. This argument has been thoroughly reviewed but is not found persuasive as Berlin's method clearly indicates that distinguishing methylation and cytosine to thymine mutations are related (see column 1, lines 9-13).

The response further asserts that the teachings of Pradhan and Lopez do not teach each and every limitation as Lopez teaches that Lopez does not teach one or more cytosines is methylated in the starting DNA. This argument has been thoroughly reviewed but is not considered persuasive as Pradhan and Berlin teach the use of DNA with methylated cytosines. Thus contrary to the assertion the limitation is taught by the instant method.

The response continues this assertion by trying to differentiate the claimed invention from Pradhan's teachings of hemimethylated DNA. The response appears to

be asserting that the claims require methylation of both strands. This argument has been thoroughly reviewed but is not considered persuasive as the specification does not set forth a limiting definition of "said DNA being methylated." Thus being methylated is being the broadest reasonable interpretation of a DNA with a methyl cytosine. Thus the hemimethylation of Pradhan teaches this limitation. Further the teachings of Berlin and Lopez of the use of genomic DNA at least renders the use of methylated DNA obvious as Berlin teaches cytosine methylation is the most common modification in eukaryotic cells, thus rendering the use genomic DNA of eukaryotic cells with methyl cytosine obvious.

The response concludes it arguments to the teachings of Lopez and Pradhan by noting that Lopez and Pradhan do not teach detection of methylation status to deduce the methylation status of the provided DNA. This argument has been thoroughly reviewed but is not considered persuasive as this limitation was added by amendment and the teachings of Berlin address this limitation.

3. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) and Berlin et al (WO01/27317, published 4/1/2001) as applied to claims 1-6, 9, and 10 above, and further in view of Shatkin et al (US Patent 6312926).

The teachings of Lopez, Pradhan and Berlin are set forth above. Lopez, Pradhan and Berlin do not teach the methyltransferase immobilized on a solid support.

However, Shatkin et al teaches the use of hMET (methyl transferase) immobilized on protein G beads for washing assays (see column 24, lines 3-12).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Lopez, Pradhan and Berlin method of amplifying genomic DNA while maintaining genomic methylation patterns with immobilized methyltransferase taught by Shatkin, because Shatkin teaches immobilization allows washing of assays. The ordinary artisan would be motivated to improve Lopez, Pradhan and Berlin method of amplifying genomic DNA while maintaining genomic methylation patterns with immobilized methyltransferase or polymerases as taught by Shatkin, because Shatkin teaches immobilization allows washing of assay and detection of protein interactions.

Response to Arguments

The response of 11/24/2008 asserts that Shatkin et al does not cure all of the deficiencies of Lopez, Pradhan and Berlin, as previously presented in the response. These arguments have been thoroughly reviewed but are not considered persuasive because as discussed above Lopez, Pradhan and Berlin do render the instant claims obvious as the combination would result in a method of amplifying genomic DNA wherein the methylation status of the genomic DNA is maintained. The response does not set forth any other arguments to this rejection, thus this rejection is maintained.

4. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) and Berlin et al (WO01/27317, published 4/1/2001)

as applied to claims 1-6, 9, and 10 above, and further in view of Stemple et al (WO/2000/53805).

The teachings of Lopez, Pradhan and Berlin are set forth above. Lopez, Pradhan and Berlin do not teach the polymerase immobilized on a solid support.

However, Stemple teaches the immobilization of a polymerase on a solid support (see page 3 lines 14-15). Stemple teaches immobilization or fixing the site of the polymerase allows assaying of multiple nucleic acids simultaneously (See page 7, lines 25-26).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Lopez, Pradhan and Berlin method of amplifying genomic DNA while maintaining genomic methylation patterns with immobilizing a polymerases as taught by Stemple, because Stemple teaches immobilization or fixing the site of the polymerase allows assaying of multiple nucleic acids simultaneously. The ordinary artisan would be motivated to improve Lopez, Pradhan and Berlin method of amplifying genomic DNA while maintaining genomic methylation patterns with immobilized polymerases as taught by Stemple, because Stemple teaches immobilization or fixing the site of the polymerase allows assaying of multiple nucleic acids simultaneously.

Reponse to Arguments

The response of 11/24/2008 that Stemple et al does not cure all of the deficiencies of Lopez, Pradhan and Berlin, as previously presented in the response. These arguments have been thoroughly reviewed but are not considered persuasive

because as discussed above Lopez, Pradhan and Berlin does render the instant claims obvious as the combination would result in a method of amplifying genomic DNA wherein the methylation status of the genomic DNA is maintained. The response does not set forth any other arguments to this rejection, thus this rejection is maintained.

5. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) and Berlin et al (WO01/27317, published 4/1/2001) as applied to claims 1-6, 9, and 10 above, and further in view of Gonzalgo et al (US Patent 6251594).

The teachings of Lopez, Pradhan and Berlin are set forth above. Lopez, Pradhan and Berlin do not teach the use of bisulphate solution to distinguish methylation status of cytosine bases.

However, Gonzalgo et al teach the use of bisulphite to distinguish methylated and unmethylated cytosines (column 7, lines 5-6). Gonzalgo teaches the use of bisulphite is quantitative, does not use restriction enzymes, and allows multiplexing (see column 7, lines 7-10).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Lopez, Pradhan and Berlin method of amplifying genomic DNA while maintaining and distinguishing genomic methylation patterns by use bisulphite solutions taught by Gonzalgo, because Gonazalgo teaches the use of bisulphate is quantitative, does not use restriction enzymes, and allows multiplexing. The ordinary artisan would be motivated to improve Lopez, Pradhan and

Berlin method because, the use of bisulphite is quantitative, does not use restriction enzymes, and allows multiplexing. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

Reponse to Arguments

The response of 11/242008 that Gonzalgo et al does not cure all of the deficiencies of Lopez, Pradhan and Berlin, as previously presented in the response. These arguments have been thoroughly reviewed but are not considered persuasive because as discussed above Lopez, Pradhan and Berlin does render the instant claims obvious as the combination would result in a method of amplifying by PCR genomic DNA wherein the methylation status of the genomic DNA is maintained. The response does not set forth any other arguments to this rejection, thus this rejection is maintained.

Summary

No claims are allowed.

Conclusions

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C. POHNERT whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Sarae Bausch/
Primary Examiner, Art Unit 1634